JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 8, NO. 1, 2015

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2014.09.008

EDITORIAL COMMENT

The THUNDER Trial Results

Clearing the Way or Ushering the Storm?*

Michael R. Jaff, DO

With the overwhelming expansion of diabetes mellitus across the world (1), it is of no surprise that peripheral artery disease (PAD) is now a worldwide health hazard (2). With improved diagnostic methods and increasing awareness, more patients are being considered for revascularization strategies. Classically, revascularization in the form of surgical bypass was reserved for patients with manifestations of critical limb ischemia (rest pain, nonhealing ischemic ulcerations, gangrene). With the rapid advances in minimally invasive technologies over the past 2 decades, "endovascular first" strategies have become prevalent. As one observes the evolution of devices from uncoated percutaneous transluminal angioplasty (3), bare nitinol stents (4), atherectomy (5), to drug-eluting stents (6), optimism for our ability to improve functional limitations and reduce the risk of limb loss has increased.

The ability to coat a balloon angioplasty catheter with an antiproliferative agent, however, has resulted in tremendous anticipation and enthusiasm by investigators and clinicians alike as a potential primary management of femoropopliteal PAD. This was sparked by the initial publication of the THUNDER (Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries) trial (7). In this pilot randomized trial, the primary endpoint of late lumen loss (a measure adopted from percutaneous coronary intervention trials) favored the balloon catheter coated with a concentrated film of paclitaxel. In this issue of *JACC: Cardiovascular Interventions*, the investigators extend the experience from the THUNDER trial by reporting 5-year outcomes (8). The authors, who represent some of the most important and influential PAD investigators worldwide, continue to expand our knowledge of the role of interventional management in patients with symptomatic PAD.

SEE PAGE 102

Only 2 of the 3 previously randomized arms in the THUNDER trial were included in this analysis, representing 102 patients. Unfortunately, this follow-up was not always performed with an in-person evaluation, but rather via telephone assessments. This immediately limits our ability to generalize these results to larger patient cohorts. In addition, formal anatomic follow-up was not mandated in all patients at 5 years, and therefore, only those patients who actually had arteriography and/or duplex ultrasonography and could actually obtain those images were analyzed. Independent core laboratories did not interpret these images.

The authors do a commendable job of demonstrating the consistent advantages of the drug-coated balloon to bare balloon angioplasty, including a reduction in late lumen loss, fewer target lesion revascularizations (TLR), longer time periods from the initial intervention to TLR, and despite the small numbers and limitations of the analysis, improved binary patency at 5 years. These impressive findings were associated with no increase in adverse events, including arterial toxicity, amputations, or mortality rates.

The combination of devices and drugs for the management of PAD appears to hold considerable appeal for clinicians, researchers, and commercial manufacturers alike (9). Although the results of drug-eluting stents are superior to percutaneous transluminal angioplasty (6), there remain concerns about permanent implantable devices. Bioresorbable scaffolds hold tremendous hope (10); however, at least in

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. Dr. Jaff is a noncompensated advisor to Abbott Vascular, Boston Scientific, Cordis, Covidien Vascular, Medtronic Vascular; a paid consultant to Cardinal Health; an equity shareholder of PQ Bypass; and a board member of VIVA Physicians, a 501 c 3 not-for-profit education and research organization.

the peripheral artery segments, no large-scale trials are near completion, and the early results are awaiting peer-reviewed publication.

Drug-coated balloons, however, have been widely available in Europe, and the first trial data presented to a U.S. Food and Drug Administration panel was completed earlier this summer (11). Another large-scale randomized trial presented its data at an international meeting in April 2014 (12). It is therefore anticipated that drug-coated balloons will enter the U.S. marketplace within the next 12 to 18 months.

The enthusiasm for drug-coated balloons rests with the lack of a permanent implantable device, an antiproliferative agent to lessen restenosis, and the ability to offer a full spectrum of revascularization strategies should the initial intervention fail. With the recently reported randomized data (still pending peer-reviewed publication at the time this paper was written) and the results of the THUNDER 5-year follow-up, it appears that drug-coated balloons will have an impact on the patients with PAD who require intervention. One factor that will undoubtedly impact the uptake of this class of technologies is the cost effectiveness compared with other revascularization and medical strategies. The data on this are quite limited but suggest a potential advantage to payers because of the low TLR rates of drug-coated balloons (13).

The 5-year THUNDER trial data unfortunately do not shed light on the actual cost impact of the 2 arms reported. In addition, we have no insights into the optimal drug, the optimal dose concentration of the drug, effective adjuvant medical therapy, including the role of antiplatelet therapy, cholesterol lowering, and tobacco cessation. Finally, there remain no comparisons of drug-coated balloons for treatment of claudication as a result of femoropopliteal artery disease to supervised exercise and optimal medical therapy, as studied in iliac artery disease (14).

Are there lessons here? Undoubtedly. We need to determine what endpoints for trials in patients with claudication truly matter, and to which constituency. Each trial must demonstrate objective functional benefits following intervention, as that is why patients want these procedures—they choose to walk farther with less discomfort. We are obligated, in this era of accountable care, to measure episodes of care and total medical expense, and consider comparative costs and outcomes. We need to consider what is really *cost effective* for the claudicant (15). If we don't, I am afraid that the THUNDER we hear will not represent advancing data but rather, doors closing to adoption of new technologies and outcomes by payers, ultimately limiting options for our PAD patients.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Michael R. Jaff, Massachusetts General Hospital, 55 Fruit Street, Warren 905, Boston, Massachusetts 02114. E-mail: mjaff@partners.org.

REFERENCES

1. Beagley J, Guariguata L, Weil C, Motala AA. Global estimates of undiagnosed diabetes in adults. Diabetes Res Clin Pract 2014;103:150–60.

2. Fowkes FGR, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet 2013;382:1329–40.

3. Rocha Singh KJ, Jaff MR, Crabtree TR, Block DA, Ansel G. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. Catheter Cardiovasc Interv 2007;69:910–9.

4. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery: twelve-month results from the RESILIENT randomized trial. Circ Cardiovasc Interv 2010;3:267–76.

5. McKinsey JF, Zeller T, Rocha Singh KJ, Jaff MR, Garcia LA. Lower extremity revascularization using directional atherectomy: 12-month prospective results of the DEFINITIVE LE study. J Am Coll Cardiol Intv 2014;7:923–33.

6. Dake MD, Ansel GM, Jaff MR, et al. Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions: 2-year follow-up from the Zilver PTX randomized and single-arm clinical studies. J Am Coll Cardiol 2013;61:2417–27.

7. Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. N Engl J Med 2008;358:689–99.

8. Tepe G, Schnorr B, Albrecht T, et al. Angioplasty of femoral-popliteal arteries with drug-coated balloons: 5-year follow-up of the THUNDER trial. J Am Coll Cardiol Intv 2015;8:102–8.

9. Sarode K, Spelber DA, Bhatt DL, et al. Drug delivering technology for endovascular management of infrainguinal peripheral artery disease. J Am Coll Cardiol Intv 2014;7:827–39.

10. Werner M. Bioresorbable scaffolds for the SFA: new developments. J Cardiovasc Surg 2014;55:455–9.

11. Circulatory System Devices Advisory Panel Provides a Unanimous Favorable Recommendation to FDA for the Lutonix® Drug Coated Balloon. June 12, 2014. MarketWatch website. Available at: http://www.marketwatch.com/story/circulatory-system-devices-advisory-panel-provides-a-unanimous-favorable-recommendation-to-fda-for-the-lutonix-drug-coated-balloon-2014-06-12. Accessed October 15, 2014.

12. IN.PACT SFA One-Year Results: Drug-Eluting Balloon Outperforms Angioplasty With Lower Reintervention Rates and Superior Patency. April 6, 2014. Charing Cross Symposium website. Available at: http://www.cxvascular.com/cx-latest-news/cx-latest-news/cx-2014-audience-recognises-the-impact-of-drug-eluting-balloons. Accessed October 15, 2014.

13. Pietzsch JB, Geisler BP, Garner AM, Zeller T, Jaff MR. Economic analysis of endovascular interventions for femoropopliteal arterial disease: a systematic review and budget impact model for the United States and Germany. Catheter Cardiovasc Interv 2014;84:546–54.

14. Murphy TP, Cutlip DE, Regensteiner JG, et al. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) Trial. Circulation 2012;125:130–9.

15. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—The curious resilience of the $50,000-per-QALY threshold. N Engl J Med 2014;371:796–7.

KEY WORDS drug coated balloons, peripheral artery disease, restenosis